



photon

# **Impact of Baseline Central Retinal Thickness on Visual and Anatomic Outcomes in Patients With Diabetic Macular Edema: Post Hoc Analysis of the Phase 2/3 PHOTON Trial**

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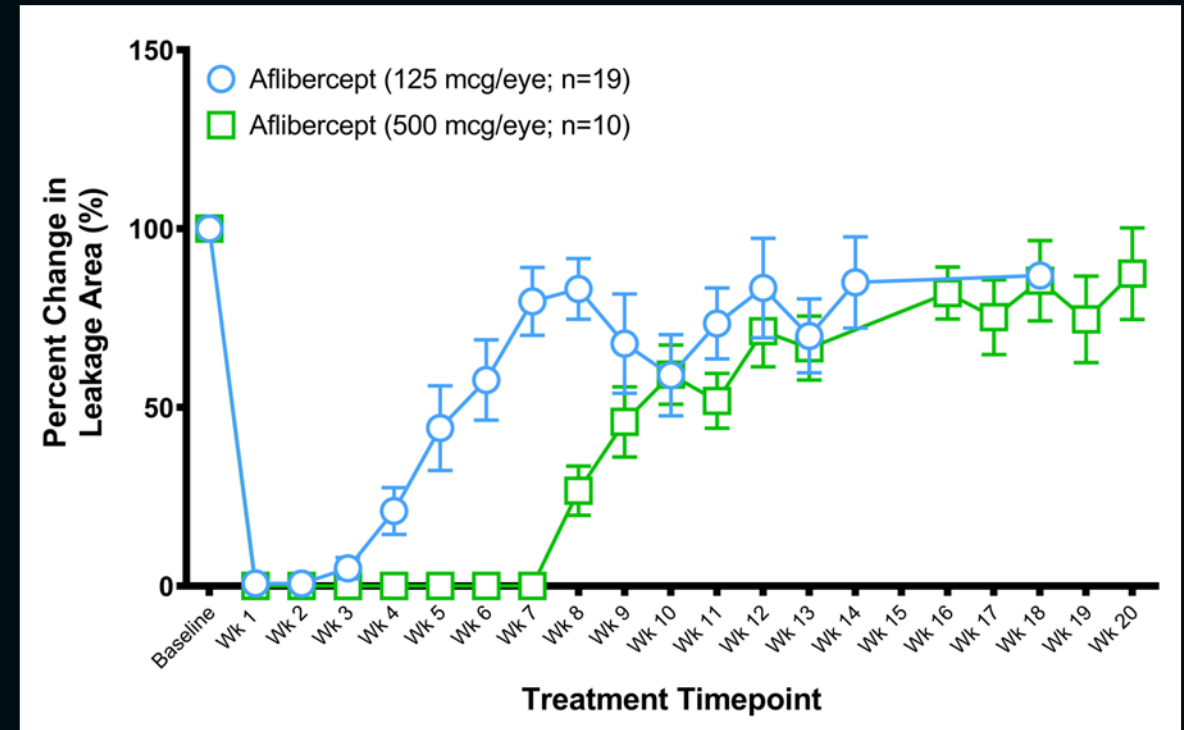
# Disclosures

- Dr. Khurana serves on the Advisory Board to Arrowhead Pharmaceuticals, Bausch + Lomb, Genentech, Inc., NGM Biopharmaceuticals, Opthea and Regeneron; and has received research funding from Annexion, Apellis, Chengdu Kanghong, Clearside Biomedical, EyePoint, Genentech, NGM Biopharmaceuticals, Opthea, Oxurion, and RegenxBio
- This trial was sponsored by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY) and co-funded by Bayer AG (Leverkusen, Germany). The sponsors participated in the design and conduct of the trial, analysis of the data, and preparation of this presentation.
- This trial includes research conducted on human patients. Institutional Review Board approval was obtained prior to study initiation
- Writing assistance by Disha Patel, PhD, Kaitlyn Scacalossi, PhD, and Stephanie Agbu, PhD, Regeneron Pharmaceuticals, Inc., is acknowledged

# Background

- Aflibercept is a fully human recombinant fusion protein that binds VEGF-A, VEGF-B, and PlGF, thereby inhibiting the activation of cognate VEGF receptors<sup>1,2</sup>
- A 4-fold increase in aflibercept dose from 125 µg to 500 µg extended the duration of complete leakage inhibition from 2 weeks to 7 weeks in the DL-AAA rabbit model<sup>3</sup>

## Dose-dependent Duration of Leakage Inhibition<sup>3</sup>



Data are mean  $\pm$  1 standard error measurement.

# PHOTON Study Design

Multi-center, randomized, double-masked study in patients with DME<sup>a</sup>  
Randomized 1 (2q8) : 2 (8q12) : 1 (8q16)

**Note: 2 mg arm received 5 initial monthly injections versus 8 mg arms, which received only 3 initial monthly injections**

**2q8**

Aflibercept 2 mg every 8 weeks  
after 5 initial monthly injections  
n=167

**8q12**

8 mg every 12 weeks after  
3 initial monthly injections  
n=328

**8q16**

8 mg every 16 weeks after  
3 initial monthly injections  
n=163

Primary endpoint at Week 48  
Mean change in BCVA (non-inferiority)

**End of study at Week 96**  
with optional 1-year extension through Week 156

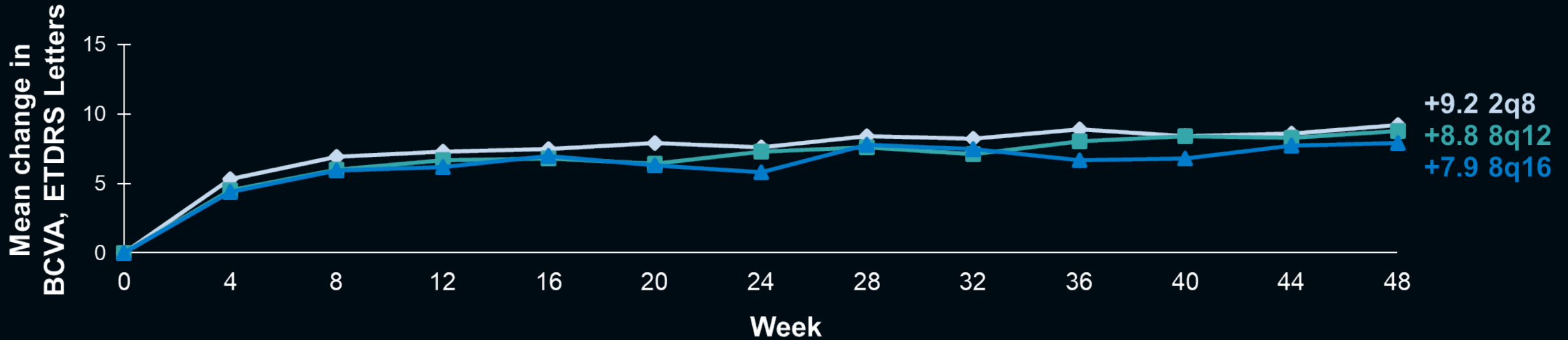
<sup>a</sup>Treatment naïve and previously treated.  
BCVA, best-corrected visual acuity; DME, diabetic macular edema.



DME

# PHOTON: 48-Week BCVA Primary Endpoint Met in Both 8 mg Groups

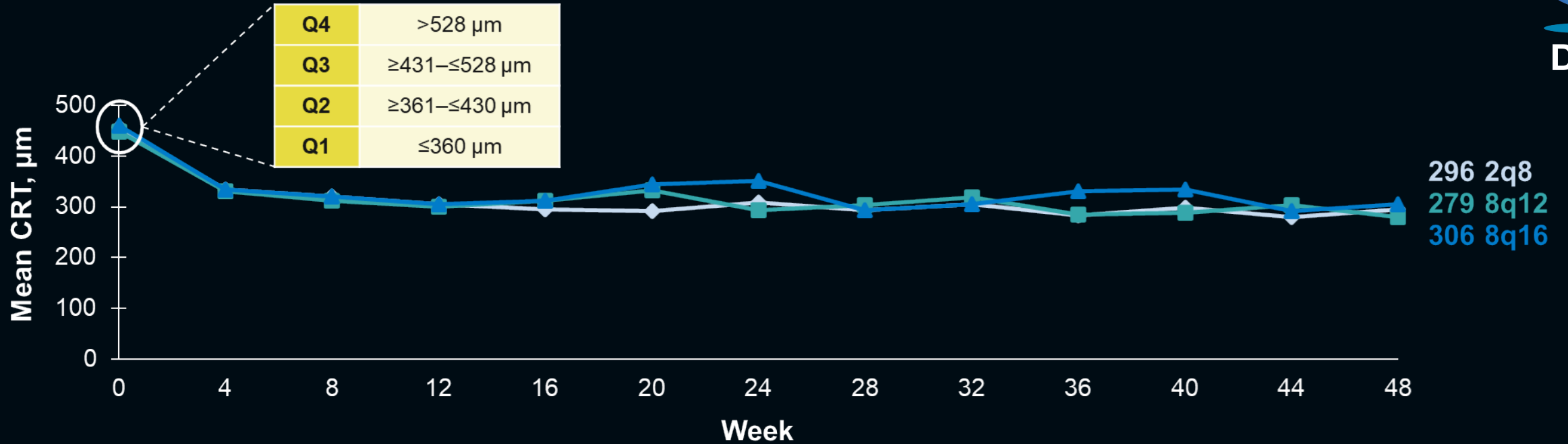
BCVA Change from Baseline<sup>a</sup>



	LS mean change from BL at Week 48 (MMRM)	Diff. in LS means vs. 2q8	2-sided 95% CI	1-sided test for non-inferiority at 4-letter margin
<b>2q8</b>	8.7			
<b>8q12</b>	8.1	<b>-0.57</b>	<b>-2.26, 1.13</b>	<b>p &lt; 0.0001</b>
<b>8q16</b>	7.2	<b>-1.44</b>	<b>-3.27, 0.39</b>	<b>p = 0.0031</b>

<sup>a</sup>Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline). ICE, intercurrent event; LS, least squares; MMRM, mixed model for repeated measures.

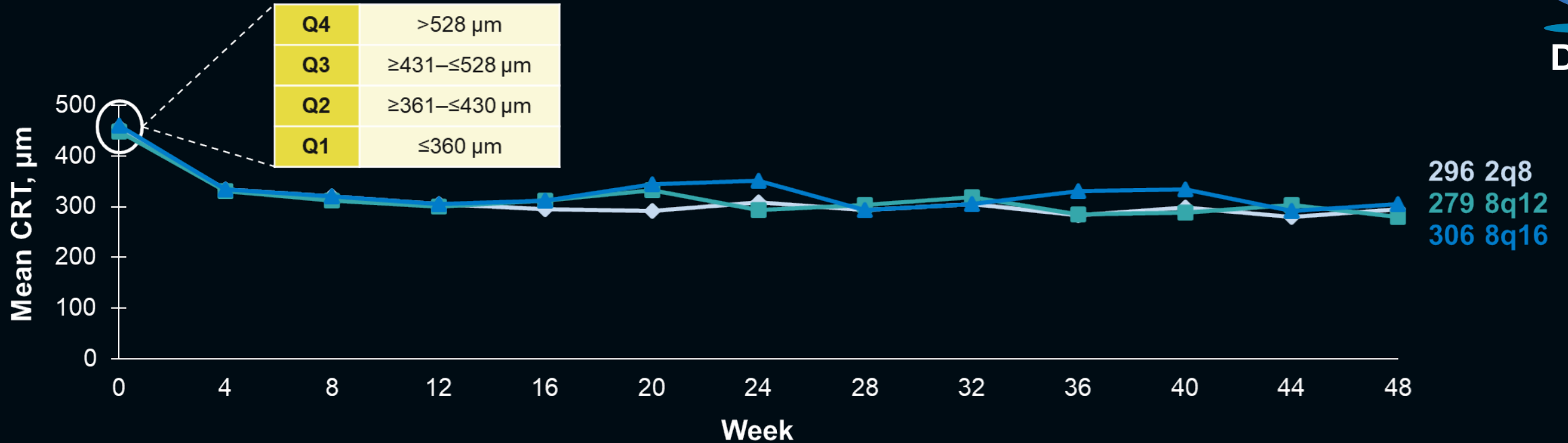
# Mean CRT Through Week 48



**This analysis evaluated the effect of aflibercept 8 mg versus 2 mg on clinical outcomes in patients with DME based on disease severity, as defined by baseline CRT**

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).  
 CRT, central retinal thickness.

# Mean CRT Through Week 48



- Analyses were descriptive and 1 patient was excluded due to missing baseline CRT
- Key outcomes assessed include:
  - Mean change in BCVA through Week 48
  - Mean change in CRT through Week 48
  - Proportion of patients who maintained their original randomized dosing intervals through Week 48

Observed values (censoring data post-ICE); FAS: 2q8 n=167; 8q12 n=328; 8q16 n=163 (at baseline).  
 CRT, central retinal thickness.

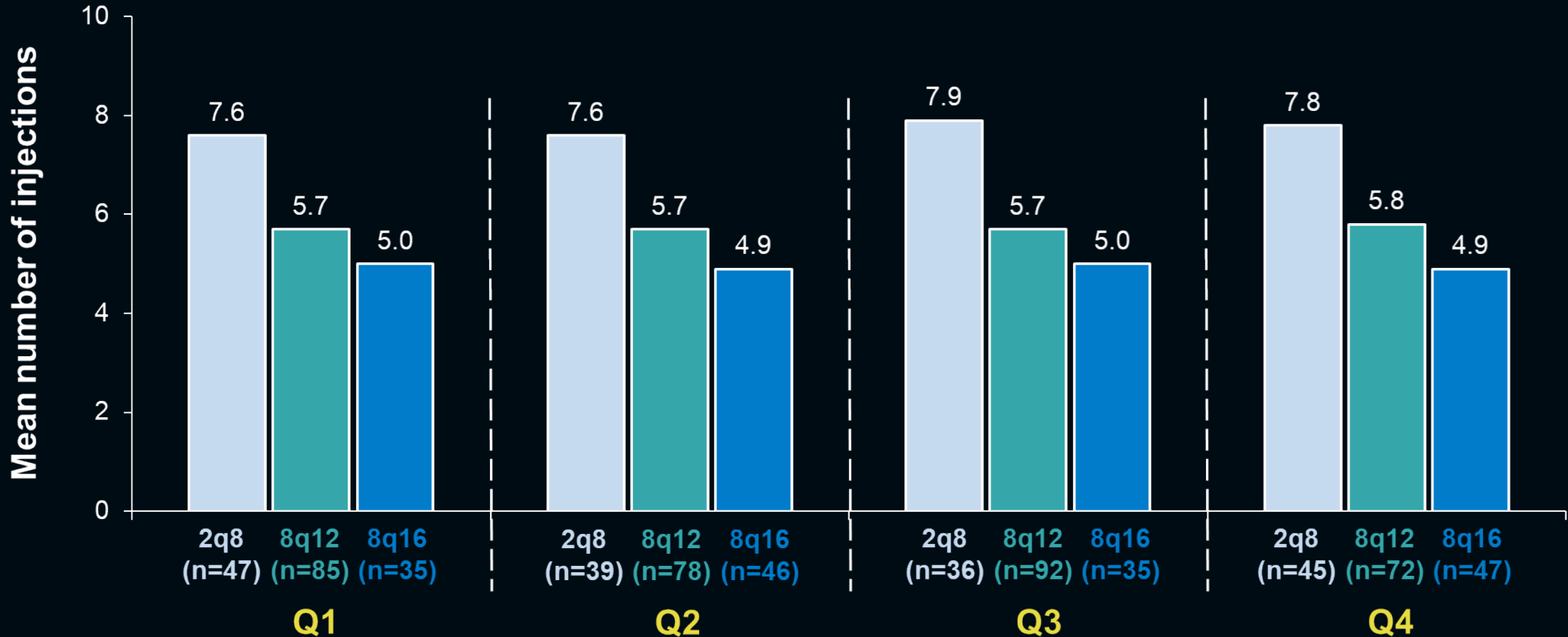
# Baseline Characteristics by Baseline CRT Quartiles

	Q1: $\leq 360 \mu\text{m}$ (n=167)			Q2: $\geq 361 - \leq 430 \mu\text{m}$ (n=163)			Q3: $\geq 431 - \leq 528 \mu\text{m}$ (n=163)			Q4: $> 528 \mu\text{m}$ (n=164)		
	2q8 (n=47)	8q12 (n=85)	8q16 (n=35)	2q8 (n=39)	8q12 (n=78)	8q16 (n=46)	2q8 (n=36)	8q12 (n=92)	8q16 (n=35)	2q8 (n=45)	8q12 (n=72)	8q16 (n=47)
Age, years	63.3 (10.7)	61.7 (10.8)	62.9 (9.5)	64.1 (8.7)	63.9 (10.8)	62.5 (9.1)	63.9 (8.5)	62.0 (9.9)	60.4 (9.8)	61.2 (10.6)	60.8 (13.2)	61.4 (9.8)
Male, n (%)	28 (59.6)	56 (65.9)	21 (60.0)	17 (43.6)	47 (60.3)	26 (56.5)	18 (50.0)	51 (55.4)	22 (62.9)	29 (64.4)	55 (76.4)	30 (63.8)
Duration of diabetes, years	18.2 (11.6)	15.3 (9.6)	18.9 (12.5)	16.8 (9.8)	16.6 (11.1)	14.4 (10.1)	14.1 (9.31)	14.3 (9.4)	14.9 (9.0)	14.3 (8.8)	14.2 (9.7)	15.1 (10.7)
BCVA, ETDRS letters	64.8 (9.9)	66.6 (7.8)	68.4 (7.1)	63.1 (10.6)	66.1 (10.1)	64.0 (11.3)	61.3 (9.8)	64.0 (8.2)	62.4 (11.3)	56.7 (12.8)	57.4 (11.5)	53.1 (10.8)
CRT, $\mu\text{m}$	320.0 (22.1)	318.7 (26.4)	326.1 (23.9)	390.3 (18.6)	391.6 (21.3)	394.2 (19.4)	475.3 (32.5)	475.0 (29.1)	479.3 (28.5)	644.2 (128.2)	632.4 (114.8)	610.9 (77.5)

FAS.  
 Unless otherwise specified, values shown represent mean (SD).  
 ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set.



# Treatment Exposure to Week 48 by Baseline CRT Quartiles



FAS, observed cases.

Q1:  $\leq 360 \mu\text{m}$ ; Q2:  $\geq 361 - \leq 430 \mu\text{m}$ ; Q3:  $\geq 431 - \leq 528 \mu\text{m}$ ; Q4:  $> 528 \mu\text{m}$ .



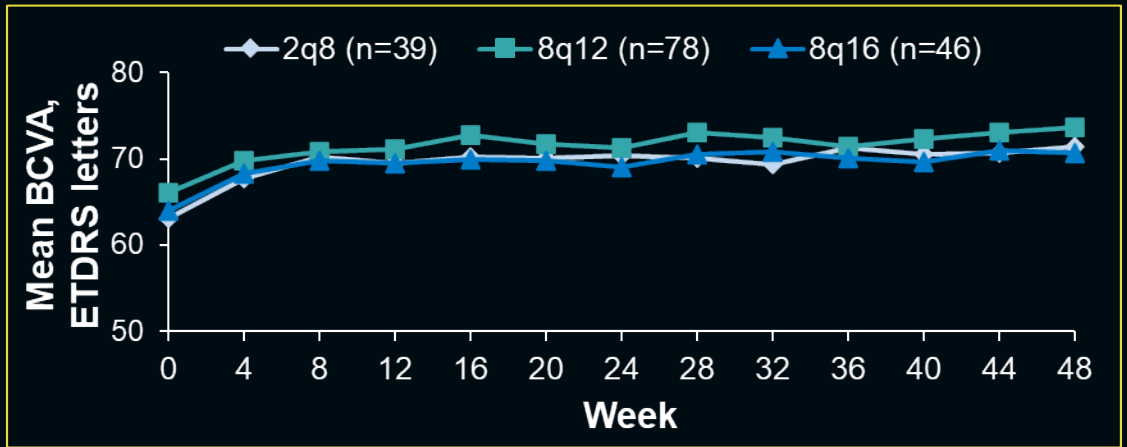
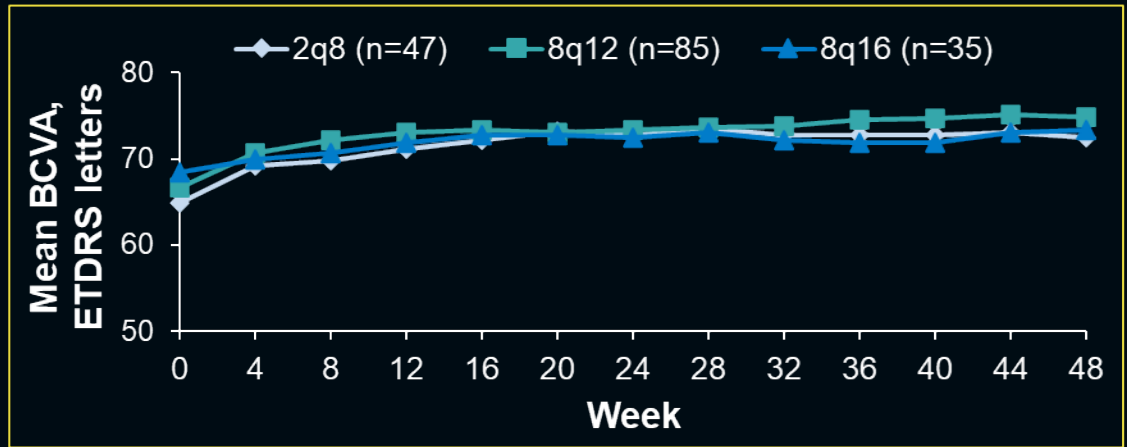
# Mean BCVA and CRT Through Week 48 in Baseline CRT Q1 and Q2

DME

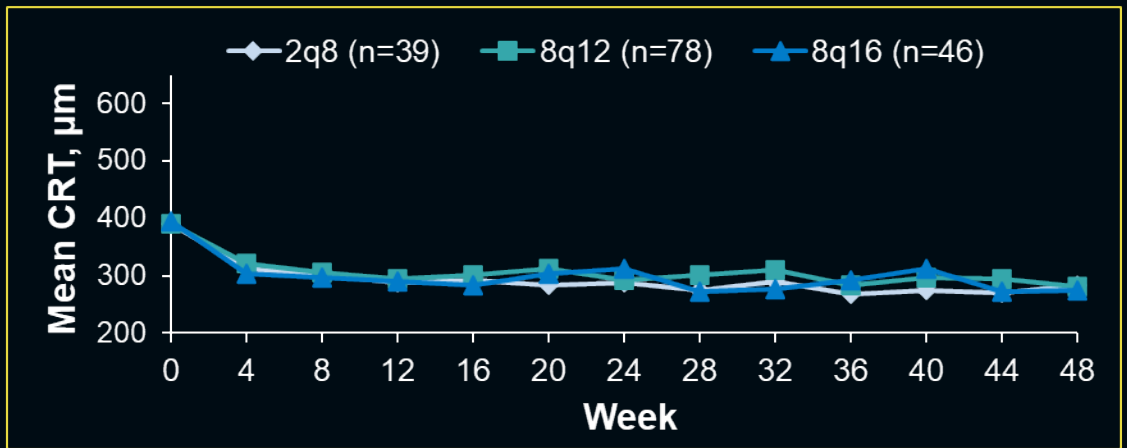
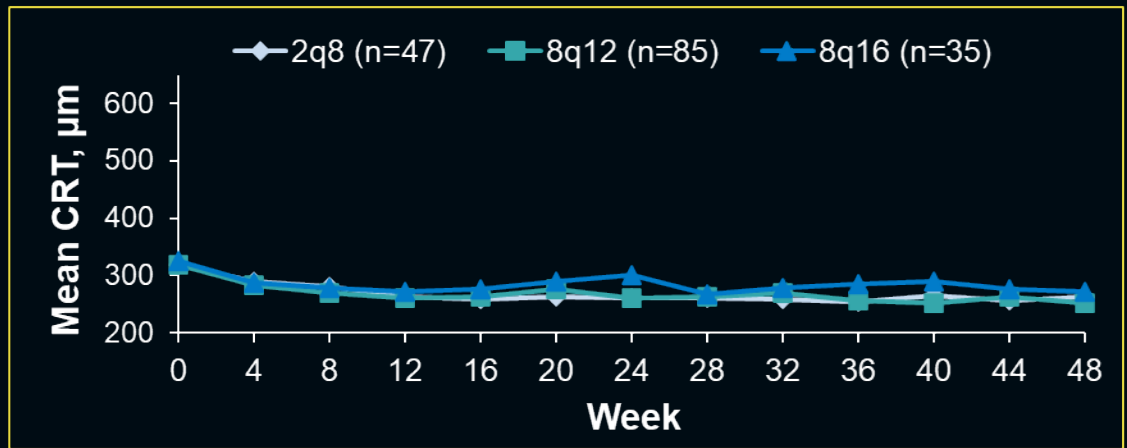
Q1:  $\leq 360 \mu\text{m}$

Q2:  $\geq 361 - \leq 430 \mu\text{m}$

BCVA



CRT



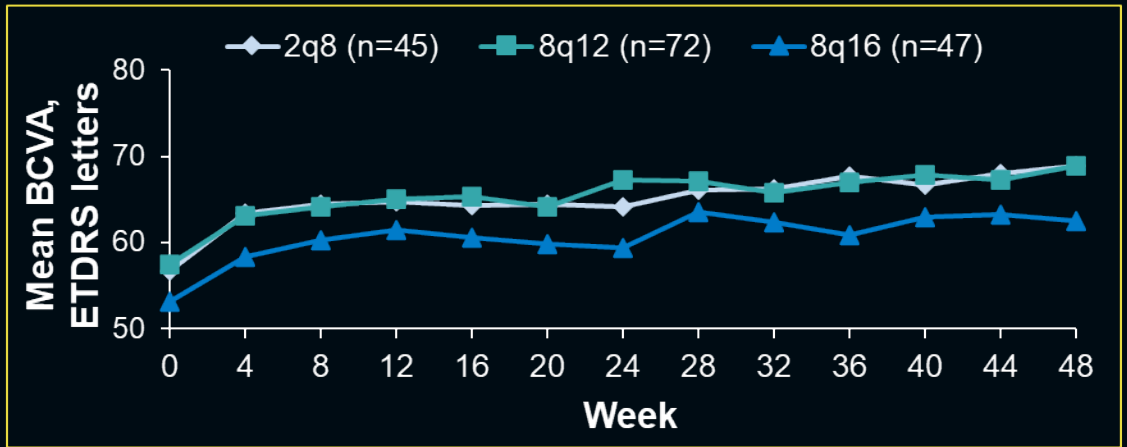
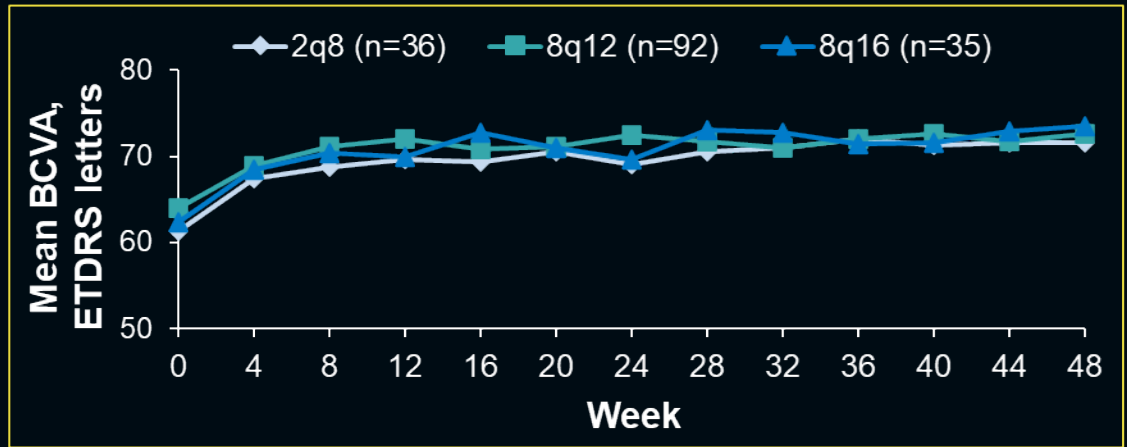
# Mean BCVA and CRT Through Week 48 in Baseline CRT Q3 and Q4

DME

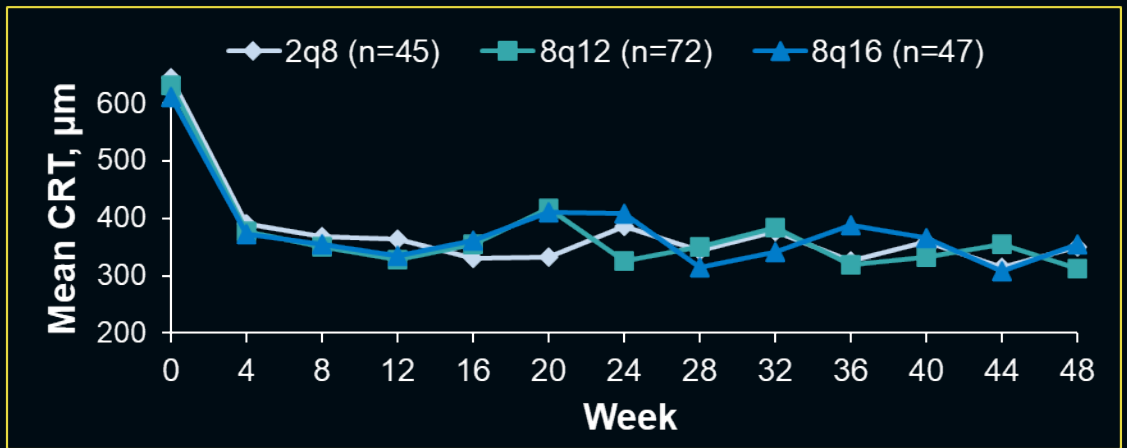
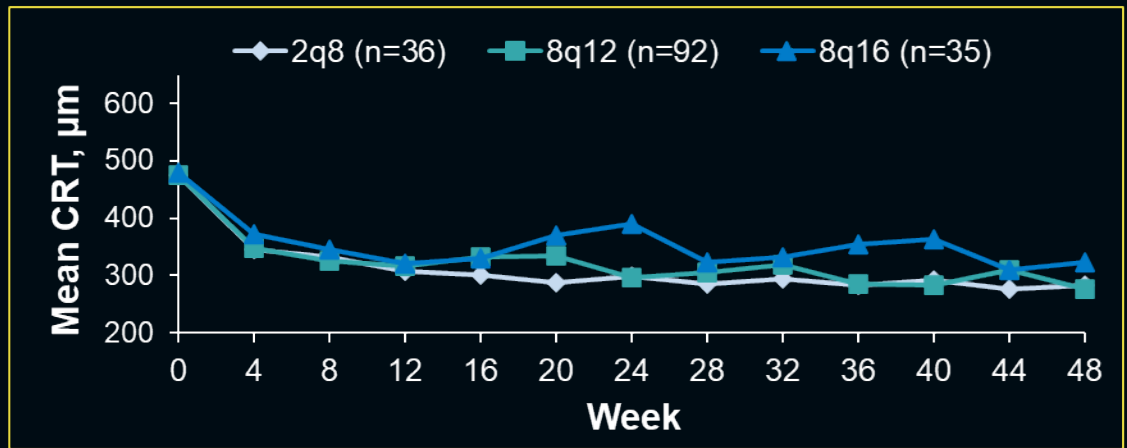
Q3:  $\geq 431 - \leq 528 \mu\text{m}$

Q4:  $> 528 \mu\text{m}$

BCVA

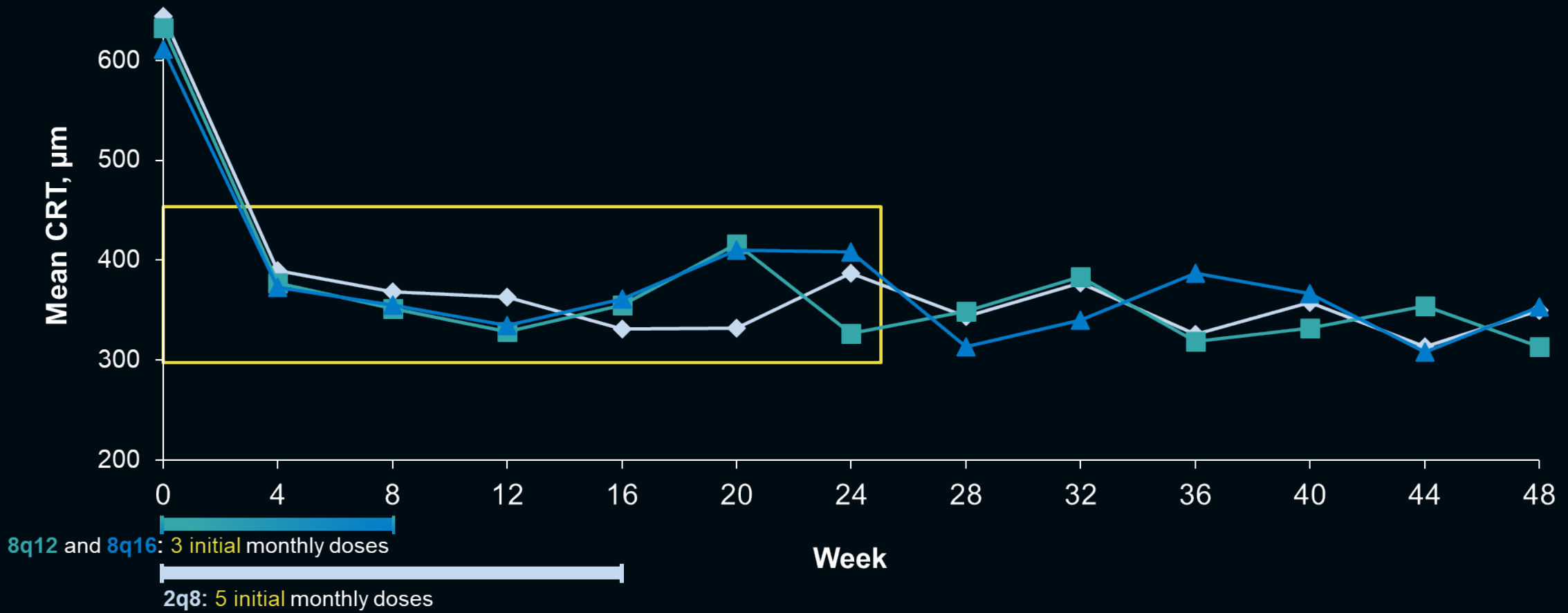


CRT



# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4

◆ 2q8 (n=45)   ■ 8q12 (n=72)   ▲ 8q16 (n=47)

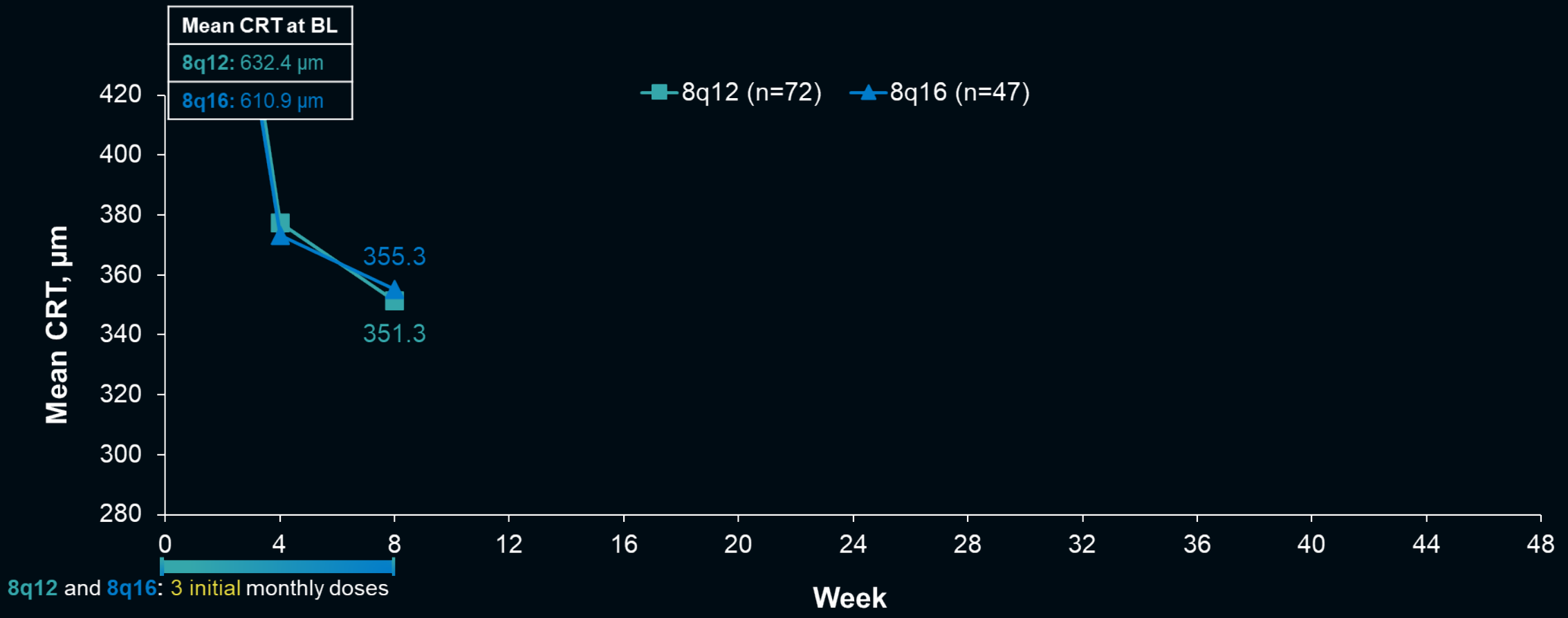


Q4 baseline CRT: >528 µm.  
FAS, observed cases.



DME

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4

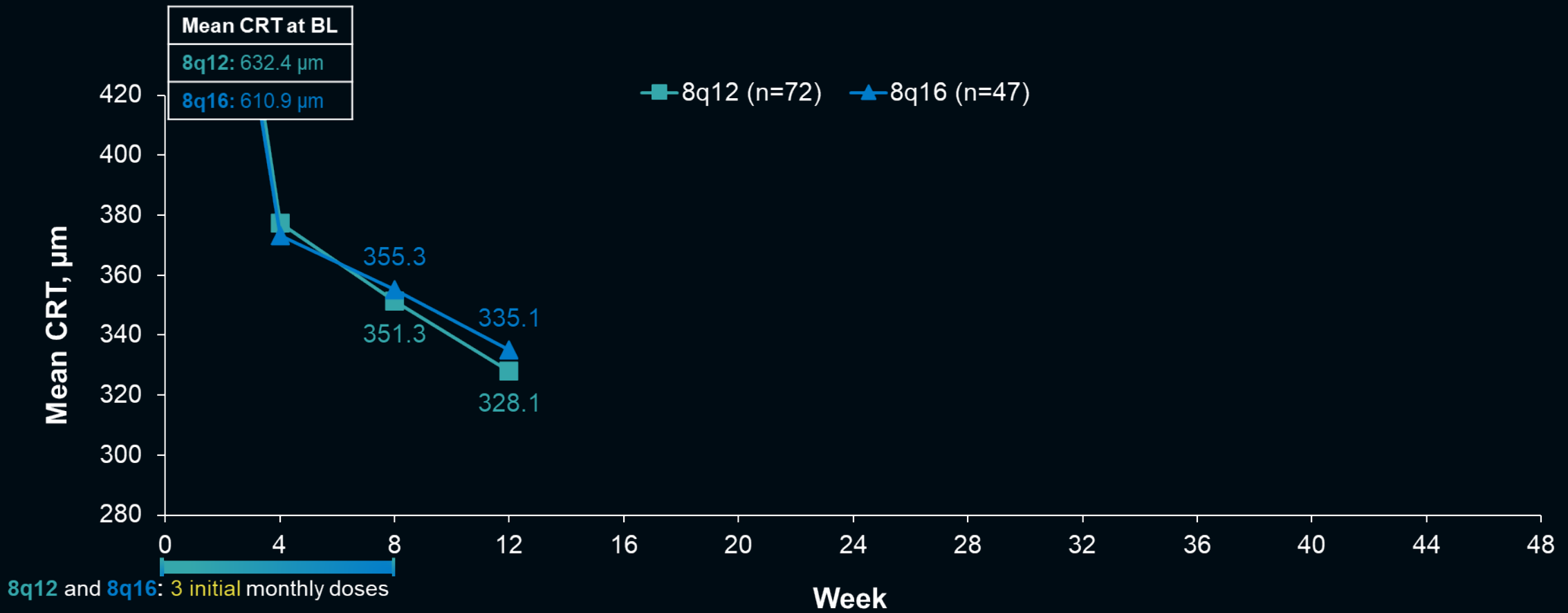


Q4 baseline CRT: >528 µm.  
FAS, observed cases.



DME

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4

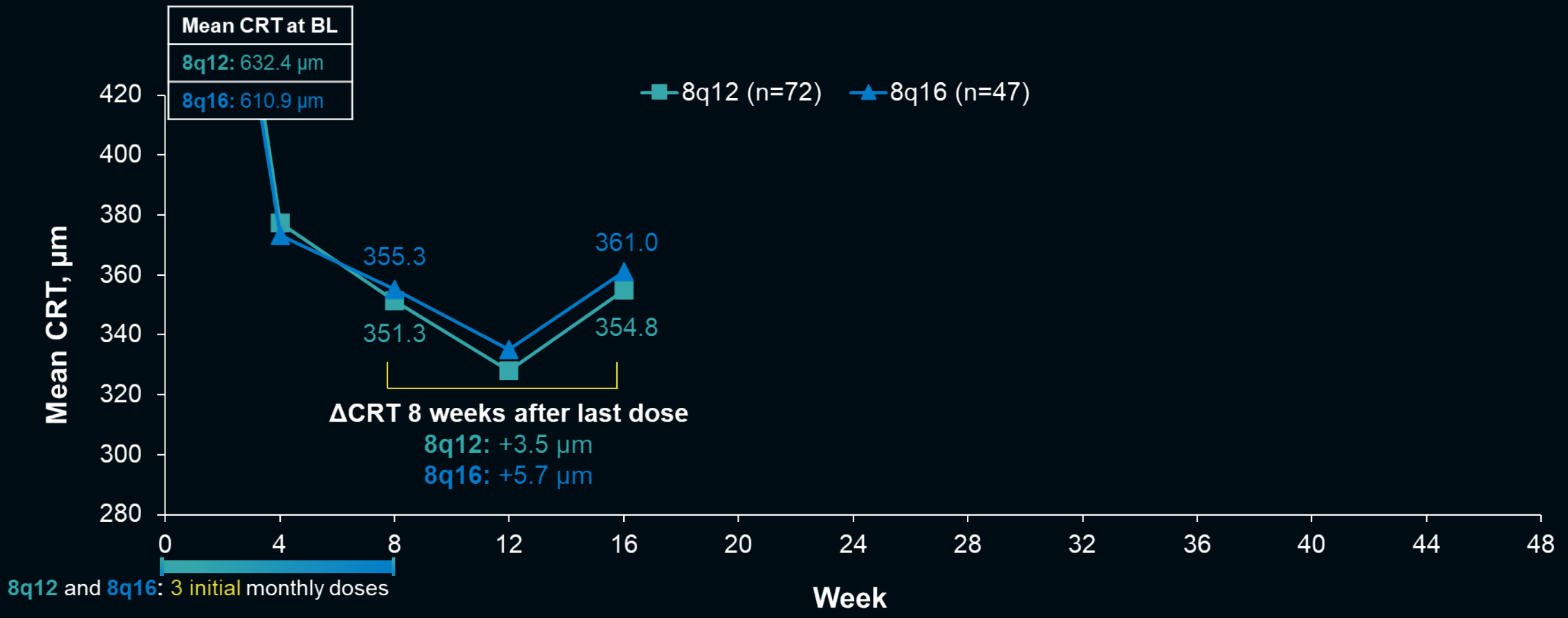


Q4 baseline CRT: >528 µm.  
FAS, observed cases.



DME

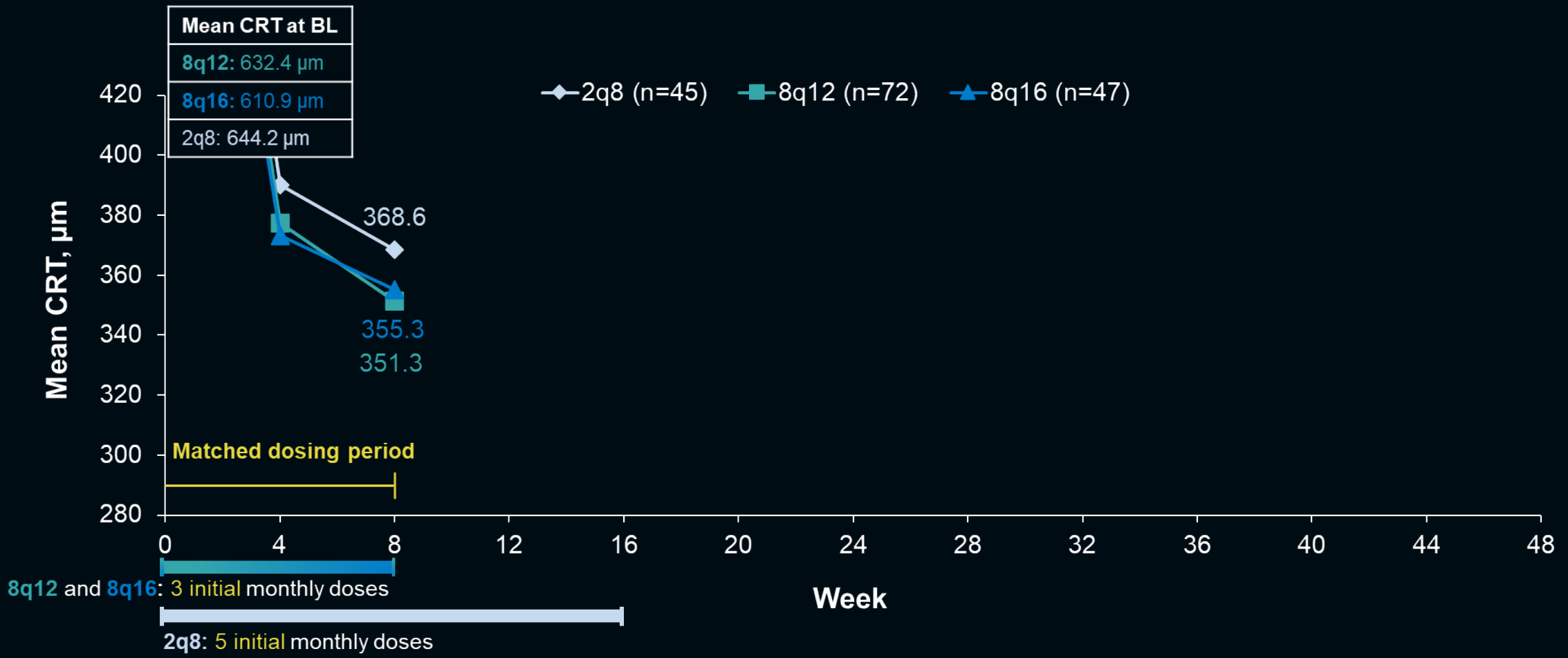
# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4



**CRT for 8q12 and 8q16 groups was similar 8 weeks after the third monthly dose**

Q4 baseline CRT: >528 µm.  
FAS, observed cases.

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4



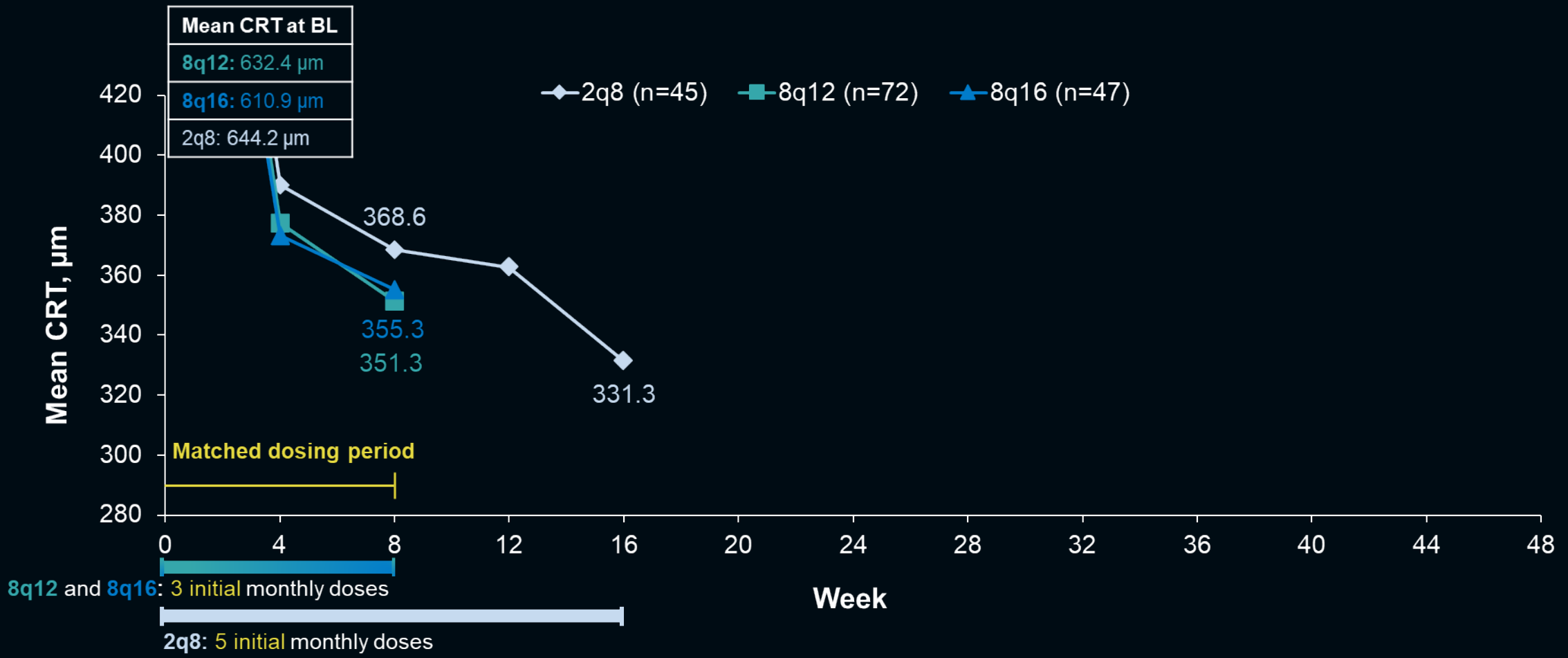
Q4 baseline CRT: >528 µm.  
FAS, observed cases.





DME

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4

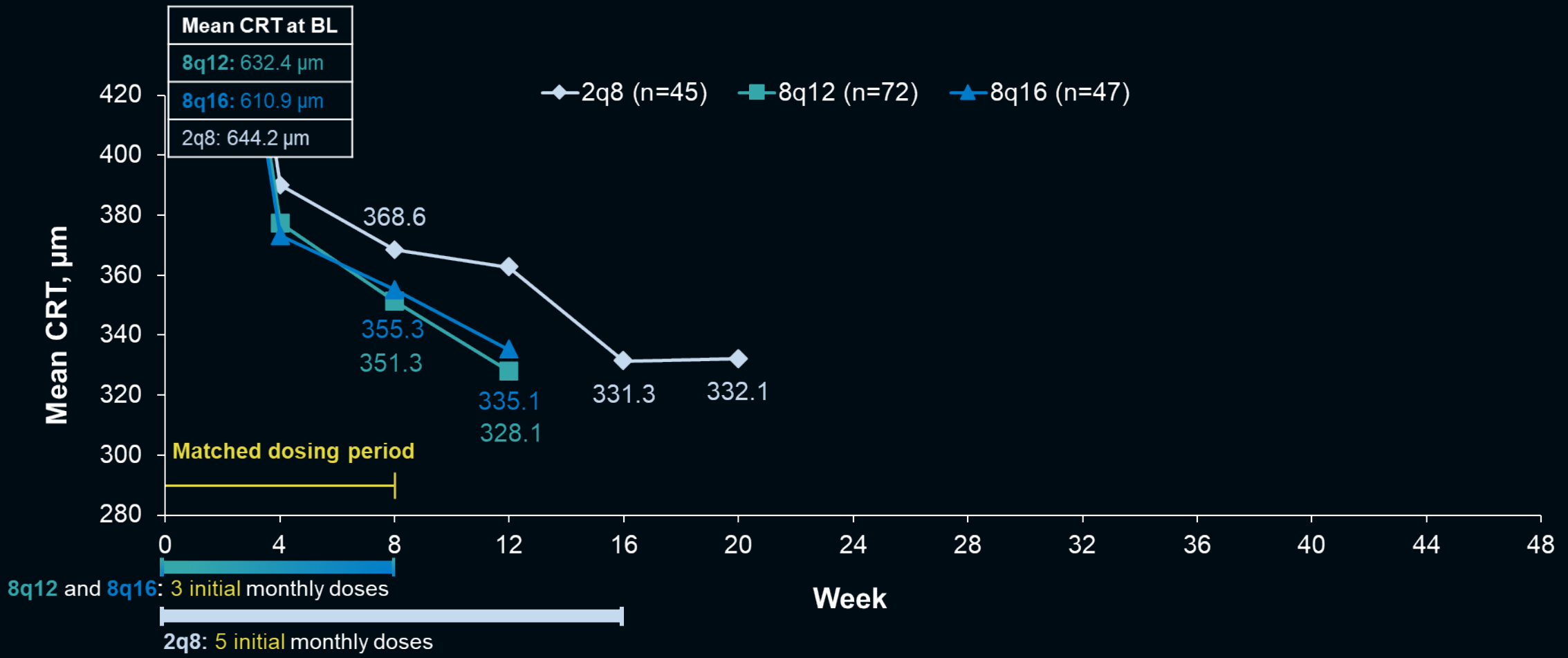


Q4 baseline CRT: >528 µm.  
FAS, observed cases.



DME

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4

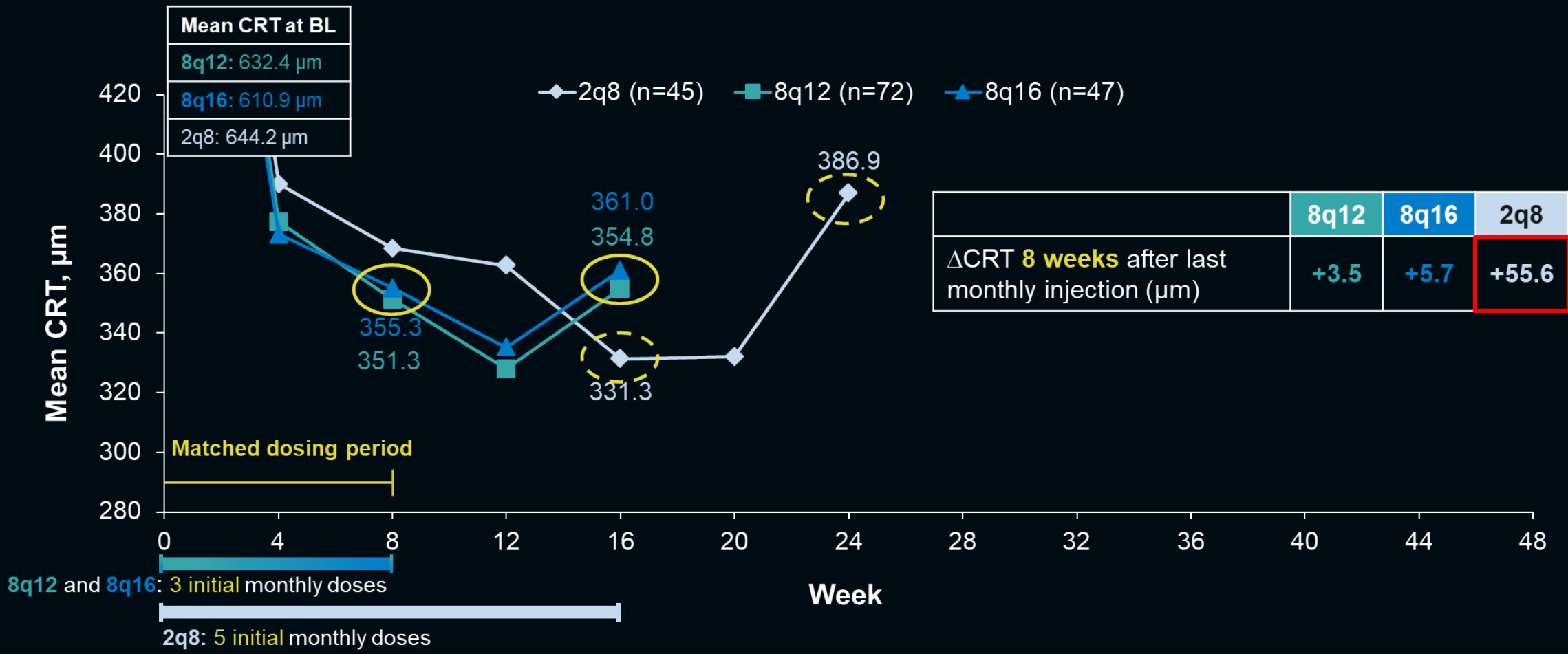


Q4 baseline CRT: >528 µm.  
FAS, observed cases.



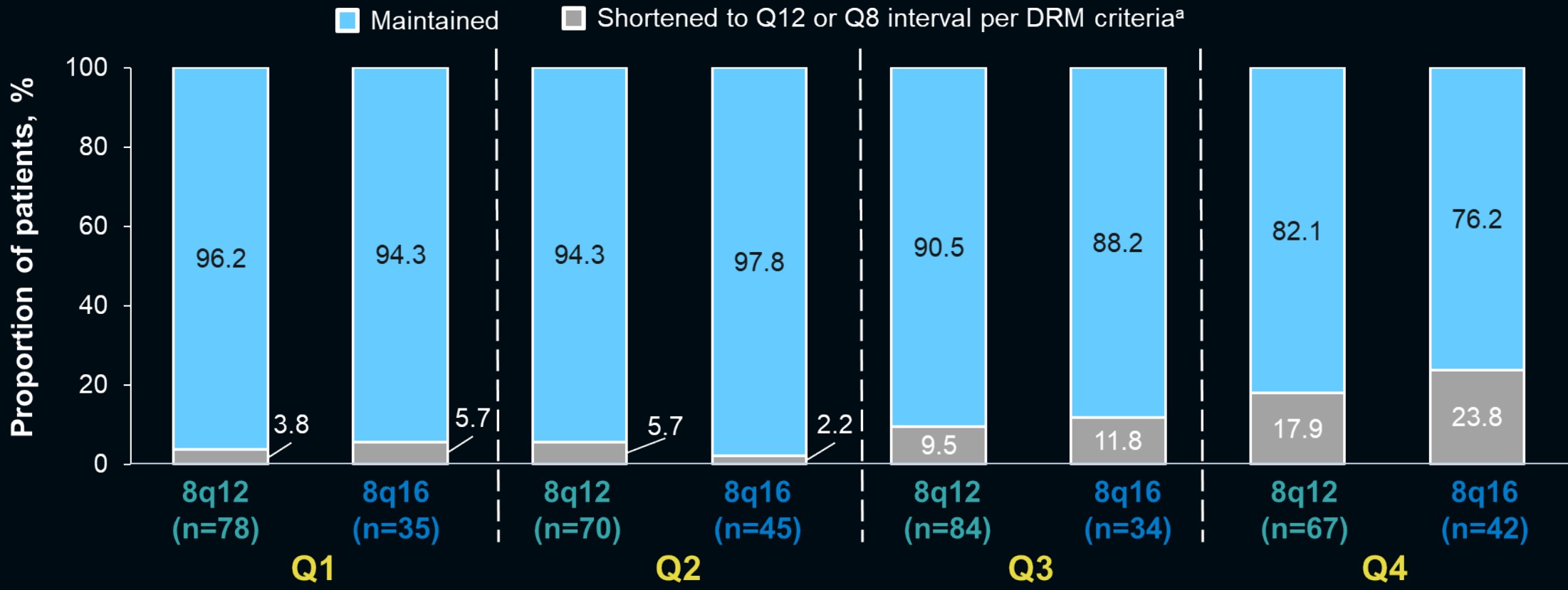
DME

# Numerically Less Fluid Reaccumulation Was Observed With Aflibercept 8 mg vs 2 mg Among Eyes in Q4



Q4 baseline CRT: >528 µm.  
FAS, observed cases.

# Majority of Aflibercept 8 mg Patients Maintained Randomized Dosing Intervals Through Week 48



**Relatively more patients in Q4 had intervals shortened through Week 48 versus Q1, Q2, and Q3**

<sup>a</sup>Dosing intervals of patients who met study-specified DRM criteria for interval shortening (loss of >10 letters from Week 12 due to persistent or worsening DME and >50- $\mu$ m increase in CRT from Week 12) at prespecified timepoints were shortened to either 12 or 8 weeks through Week 48.  
 Q1:  $\leq 360 \mu\text{m}$ ; Q2:  $\geq 361 - \leq 430 \mu\text{m}$ ; Q3:  $\geq 431 - \leq 528 \mu\text{m}$ ; Q4:  $> 528 \mu\text{m}$ .  
 FAS, patients who completed Week 48.  
 DRM, dose regimen modification.

# Conclusions

- Aflibercept 8 mg demonstrated meaningful visual and anatomic improvements in patients with DME at Week 48 across a wide range of baseline CRT values, with up to an average of 3 fewer injections compared with aflibercept 2 mg
- In eyes with baseline CRT  $>528$   $\mu\text{m}$ , fluid reaccumulation was numerically less 8 weeks after the third initial monthly dose with aflibercept 8 mg versus 2 mg after 5 initial monthly doses, suggesting a more durable treatment effect